

## CLAIMS

1. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment, with the proviso that:
  - (a) for the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia or refractory schizophrenia, the 5-HT2C receptor antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;
  - (b) for the indications cognitive dysfunction in schizophrenia or mild cognitive impairment, the 5-HT2C receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and
  - (c) for the treatment of schizophrenic suicidality, the 5-HT2C receptor antagonist is other than clozapine.
2. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of negative symptoms of schizophrenia, with the proviso that the antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.
3. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of cognitive dysfunction in schizophrenia, with the proviso that the antagonist is other than ritanserin, clozapine, fluperlapine,

loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine, deramciclane, N-desmethylderamiclane or ziprasidone.

4. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of refractory schizophrenia, with the proviso that the antagonist is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.

5. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of suicidality, with the proviso that, when the suicidality is in a schizophrenic patient, the 5-HT2C receptor antagonist is other than clozapine.

6. The use of claim 5, wherein the suicidality is in a schizophrenic patient.

7. The use of a 5-HT2C receptor antagonist in the manufacture of a medicament for the treatment of mild cognitive impairment with the proviso that the antagonist is other than deramciclane or N-desmethylderamiclane.

8. The use of any one of claims 1 to 7 wherein the 5-HT2C receptor antagonist is as described in one of WO 97/16429, WO 97/44334, US 05010078, EP 161,218, EP 401,707, EP 526,434, DE 02834114, EP 210,893, US 03580916, US 05043341, EP 620,222, EP 208,235, EP 437,790, DE 02614406, US 04338317, EP 271,013, EP 110,435, EP 398,326, WO 92/05170, WO 95/01976, WO 96/23783, WO 98/04289, WO 97/48700, WO 00/48602, WO 00/26186, WO 99/58490, WO 99/52517, WO 99/51237, WO 99/46245, WO 99/43319, WO 99/33841, WO 99/33840, WO 99/25356, WO 99/09017, WO 99/03833, WO 99/00119, WO 98/56367, WO 98/52943, WO 98/50358, WO

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00337136, EP 00332528, EP 00320983, EP 00218433 and EP  
00145494.

9. The use of any one of claims 1 to 7 in which the 5-HT2C receptor antagonist is AHR-16303B (AH Robins Co. Inc), AP-792 and AT-1015 (Ajinomoto Co. Inc.), BMS-181102 (Bristol Myers Squibb), CV-5197 (Takeda Chemical Industries Ltd), dotarizine (Ferrer Internacional SA), E-2101 (Eisai Co Ltd), eltoprazine (Solvay SA), emopamil (Knoll AG), HT-90B (Chugai Pharmaceutical Co Ltd), ICI-169369 and ICI-170809 (Zeneca Group plc), LU-26042 and LU-29066 (H Lundbeck A/S), NPC-18166 (Scios Inc), Org-38457 (NV Organon), pelanserin (Cinvestav), perbufylline (Siegfried Group), SB-206553 and SB-242084 (SmithKline Beecham), SR-46615A (Sanofi Recherche SA), SUN-9221 (Suntory Ltd) tropoxin (Russian Academy Medical Science) or YM-992 (Yamanouchi Pharmaceutical Co Ltd).

10. The use of any one of claims 1 to 7 in which the 5-HT2C receptor antagonist is Ro-60-0759, RS-102221, SDZ-SER-082, ICI-169369, deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A or LU-26042.

11. The use of claim 10 in which the 5-HT2C receptor antagonist is deramciclane, N-desmethyl-deramciclane, amesergide, sergolexole, CGS-18102A or LU-26042.

12. The use of any one of claims 5 to 7 wherein the 5-HT2C receptor antagonist is ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone.

13. The use of a compound having a relative 5-HT2C affinity of  $\geq 1.80$ , wherein the relative 5-HT2C affinity is determined according to formula I:

Formula I:

X		X
-	+	-
A		B

[wherein: X is the affinity of a compound for interaction at the 5-HT<sub>2C</sub> receptor and A and B are the average affinity values of a compound for interaction at two major sites other than the 5-HT<sub>2C</sub> receptor] in the manufacture of a medicament for the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment, with the proviso that:

- (a) for the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia or refractory schizophrenia, the compound is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;
- (b) for the indications cognitive dysfunction in schizophrenia or mild cognitive impairment, the 5-HT<sub>2C</sub> receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and
- (c) for the treatment of schizophrenic suicidality, the compound is other than clozapine.

14. A method for determining the suitability of a candidate compound for use in the treatment of negative symptoms of and/or cognitive dysfunction in schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment which comprises:

- a) assessing the affinity of the compound at the 5-HT<sub>2C</sub> receptor;

- b) assessing the affinity of the compound at at least two other major sites of said compound interaction;
- c) applying the assessed affinities to the following formula:

$$\begin{array}{c} X \\ - \\ A \end{array} + \begin{array}{c} X \\ - \\ B \end{array} = Y$$

[wherein: X is the affinity of a compound for interaction at the 5-HT<sub>2C</sub> receptor and A and B are the average affinity values of a compound for interaction at two major sites other than the 5-HT<sub>2C</sub> receptor];

and selecting compounds in which Y ≥ 1.80 as suitable compounds for the treatment of cognitive dysfunction in and/or negative symptoms of schizophrenia, refractory schizophrenia, suicidality or mild cognitive impairment, provided that:

- (a) for the treatment of cognitive dysfunction in and/or negative symptoms of schizophrenia or refractory schizophrenia, the compound selected is other than ritanserin, clozapine, fluperlapine, loxapine, ORG-5222, pipamperone, sertindole, olanzapine, zotepine or ziprasidone;
- (b) for the indications cognitive dysfunction in schizophrenia or mild cognitive impairment, the 5-HT<sub>2C</sub> receptor antagonist is other than (1R,2S,4R)-(-)-2-phenyl-2-(dimethylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane, (1R,2S,4R)-(-)-2-phenyl-2-(methylaminoethoxy)-1,7,7-trimethyl-bicyclo[2.2.1]heptane and pharmaceutically acceptable acid addition salts thereof; and
- (c) for the treatment of schizophrenic suicidality, the compound selected is other than clozapine.

15. The use of claim 13 or method of claim 14 in which A and B are different and are independently selected from the group consisting of the 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>, D<sub>1</sub>, D<sub>2-S</sub>,

D<sub>2</sub>-L, D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub> M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub>, M<sub>5</sub>, mACh, α<sub>1</sub>, α<sub>2</sub>, H<sub>1</sub> or sigma receptors.

16. The use or method of claim 15 in which A is the value for affinity at the 5-HT2A receptor.

17. The use or method of claim 15 in which B is the value for affinity at the D2 receptor.

18. Products containing a 5-HT2C receptor antagonist and a typical antipsychotic as a combined preparation for simultaneous, separate or sequential use in schizophrenia or suicidality therapy, or the treatment of mild cognitive impairment.

19. A product according to claim 18 in which the 5-HT2C receptor antagonist is identified according to the method of any one of claims 14 to 17.

20. A product according to claim 18 in which the 5-HT2C receptor antagonist is as defined in any one of claims 8 to 13.

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